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SOME ENDOCRINE MANIFESTATIONS OF CENTRAL NERVOUS SYSTEM DISEASE*

AN APPROACH TO CLINICAL NEUROENDOCRINOLOGY

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INTRODUCTION

CLINICAL neuroendocrinology, encompassing as it does the problems in man of normal and deranged central nervous system control of endocrine function as well as the effects of hormones on the brain, has a long and impressive history dating back at least to the original report of Alfred Fröhlich in 1901. Such disorders have always attracted considerable attention not only because of their intrinsic medical interest but also for the promise they hold of providing insights into the mysteries of growth, maturation, and even behavior. It is probably no exaggeration, however, to say that neuroendocrinology has fallen somewhat short of its promise, at least in clinical application. There is need to inquire why this is true and how it may be remedied.

There are certain general difficulties inherent in developing any field that straddles several more traditional disciplines, in this case

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endocrinology and the neurological sciences, for a balance must be achieved in fusing the two separate areas, requiring of the investigator considerable knowledge and a broad viewpoint. In the laboratory the natural evolution of such research, beginning as it did with an inquiry into the control of the glands of internal secretion, has given the field a strong endocrine orientation. Indeed it has only been more recently, now that the true extent of nervous system involvement has come to be realized and the endocrine propensities of the brain itself better appreciated, that a more specifically neurological orientation has developed. The imbalance persists, but continued laboratory research on such problems tends to have a unifying effect. In the clinic, however, the problems of unification and balance are even more apparent. Here traditions of training and specialization have made crossing the boundary between endocrinology on the one hand and neurology and neurosurgery on the other even more difficult and infrequent; there is no specialty of clinical neuroendocrinology per se.

To these more general obstacles must be added others related more specifically to their clinical application. Neuroendocrine disorders in man result especially from disturbances of particular regions of the brain: namely, the brainstem, hypothalamus, and limbic system. Here the pathways are somewhat diffusely organized, and they rest side by side or are intermingled with systems subserving various homeostatic, defensive, or motivational functions and others involved in arousal, attention, or consciousness itself. Small lesions are difficult to detect, while large ones may be associated with devastating neurological deficits related to the neighboring systems; indeed many such lesions are fatal. This tends to place the endocrine problems in the background or to obscure them. Even when patients are suitable for investigation, the responsible lesions are apt to reside in portions of the nervous system rather inaccessible to diagnostic and therapeutic approach. Furthermore, the endocrinopathies that result are often not obvious at the bedside. Many can be disclosed only by special examinations and tests requiring the appraisal of endocrine responses to certain specific challenges.

All these factors have tended to retard progress in clinical neuroendocrinology, particularly when compared to its experimental counterpart, so that at present it is more of a research than a clinical field. This brings us to the final difficulty, that of establishing useful communication between laboratory and clinic. At our present stage of

development the flow of information must be from the former to the latter, and experimental findings will have to serve as the source of many of the data and even of the theoretical framework within which clinical observations must be fitted.

Consequently, special efforts are called for to relate those clinical observations that are available to the increasingly sophisticated formulations of the experimental laboratory. This could serve to bring order and general relevance to an area that must still seem obscure to many clinicians. In the following account an attempt has been made in this direction, but it is scarcely more than an outline and many of its ideas are still tentative. To keep this summary manageable and not too lengthy, the scope has been confined to neuroendocrine disorders of the adenohypophysis and its target glands. Consequently most of the area concerning the neurohypophysis and fluid and electrolyte balance as well as that concerning the effect of hormones upon the brain and behavior—subjects that fully merit equal attention—have been omitted.

What follows has been divided into two parts. The first part is a synopsis of relevant anatomy and physiology taken from the experimental literature. It is a brief survey oriented around general areas of function and, because the literature is so abundant, attribution by individual citation has not been generally attempted. Instead certain broad references, many of them recent reviews or books, are listed in the first section of the bibliography. The second part deals with individual neuroendocrine syndromes, analyzed according to the preceding functional schema. Here the literature is still modest in quantity, and supporting evidence, often incomplete, is cited in the text from certain selected and more current references; these citations are listed in the second section of the bibliography.

General Neuroendocrine Functions

We may begin with an examination of the role in normal bodily economy subserved by the neuroendocrine mechanisms controlling the adenohypophysis and its target glands. Three broad areas of function can be distinguished: homeostasis, reflexes, and complex neuroendocrine responses. Homeostasis represents that type of function whose purpose is to maintain some dependent variable—a hormone or some function controlled by it—relatively constant. By neuroendocrine reflex is meant a relatively stereotyped response involving the endocrine sys-

tem as a result of some specific, temporary change in the environment. The remainder of the neuroendocrine responses are termed complex, and they involve cyclic or other more complicated temporal sequences of endocrine responses, or involve more than one hormone in a change of the over-all endocrine profile often resulting from a more general environmental change. Clearly these definitions are broad enough to overlap significantly, and some distinctions are necessarily artificial. In fact, examples come at once to mind whose classification is somewhat arbitrary and for which no strong defense can be made. Nonetheless this classification may have some merit in organizing the material, establishing anatomical-functional correlations, and in suggesting a hierarchical pattern of complexity within the neuroendocrine system. An outline and description of each will be followed by a prediction about how disordered or absent function would manifest itself. Finally the anatomical substrate upon which the function depends will be discussed.

Homeostasis

The hormone levels in the blood of some of the endocrine glands are characterized by their constancy, and their maintenance at these levels or at least between certain fixed limits, the problem of homeostasis, is largely the province of certain neuroendocrine control mechanisms. At the same time it should be pointed out that not all blood-borne hormones are characterized by such constancy, and that even some that are maintained relatively constant may be subject to intermittent or periodic deviations that will concern us later. Thus thyroid hormone levels, gonadal steroids in the male and, within daily cyclic limits, adrenal cortical hormones all remain at more or less constant levels. The concept of homeostasis is broader than this, however. In some instances, it is the stability not of the hormone but of its controlled variable that is maintained, as in the case of serum osmolality by vasopressin, or of blood sugar by insulin and somatotropin. In these instances, constancy of the controlled variable is achieved at the cost of wide fluctuations in the hormone levels, but the goal, homeostasis, is the same.

Maintenance of such stability is the function of a class of control mechanisms termed "regulators" by control-systems engineers. They are characterized by a fixed set point and a negative feedback, in some

instances continuous, in others intermittent. The minimum of components for such a system would necessarily include a detector for measuring the controlled variable (e.g., the blood sugar), a set point or established reference point, a comparator to measure any deviation of the variable from the established set point, and a corrective or error signal from the comparator suitably translated and amplified by a central device into an effective response, such as the release of somatotropin in the presence of low blood sugar.

Disorders of these homeostatic regulatory systems may be divided into two groups, those affecting the final common pathway-effector limb on the one hand and those affecting the sensor-comparator apparatus or the set point on the other. In the case of the former, the result will be a deficiency of the affected adenohypophysial hormones and those of any target endocrine glands involved. This deficiency will be proportional both to the degree of damage and to the degree of dependence of adenohypophysial function on cerebral control, which is not the same for all. The one exception will be adenohypophysial hormones under inhibitory control, which will then be produced to excess, as in the case of prolactin. In the case of the second type of disorder, damage to the sensory limb of the loop will produce a disruption of homeostasis characterized by independence between the blood levels of the controlled variable—hormone, blood sugar, etc., as the case may be —and the cerebral controlling influence. Since the feedback is negative this may result in elevated hormone levels, or levels poorly corrected after outside disturbance.

Regarding detection of such disorders, deviations from mean normal levels can be established by conventional hormone assays, provided the normal limits are narrow enough and the tests sensitive. Disorders of feedback control are better revealed by specific challenges to the homeostatic mechanism itself. The goitrogenic response to propylthiouracil, the consequence of a compensatory increase in TSH resulting from chemical blockade of thyroxin synthesis, is one such example, but one of little clinical usefulness. Another is the dexamethasone suppression test. Here the sensors are affected by a synthetic adrenal corticoid that produces potent central inhibition but does not interfere with measurement of endogenous corticoids. Inhibition normally results, with a drop of measurable endogenous corticoid production and excretion. Still another is the SU-4885 or methopyrapone disinhibition

test, in which a late stage of adrenal corticoid synthesis is chemically blocked, resulting in diminishing sensor inhibition and compensatory overproduction of ACTH and certain intermediate-stage corticoids that can be measured in urine.

While many of the homeostatic mechanisms were orginally assumed to reside in the pituitary gland itself, they are now believed to be within the hypothalamus, which must be included in the feedback loop and which possesses far more versatile information-processing capabilities than the pituitary gland alone. Our consideration of the anatomical substrate of these systems might begin with the unit that acts as intermediary between the hypothalamic control mechanisms and the adenohypophysial effector apparatus—the neurosecretory cell. Such neurones are termed neurosecretory because they possess some axons that terminate upon and discharge chemical agents into blood vessels instead of participating in ordinary neuroneural or neuromuscular synapses. Ordinarily there is histological evidence of their secretory activity.

Of the neurosecretory cells involved in mammalian adenohypophysial control the majority are believed to be located in the ventromedial hypothalamic region called the infundibulum, immediately proximal to the neurohypophysis. This region appears on the ventral surface of the brain as the tuber cinereum and a portion of the median eminence and contains the infundibular recess of the third ventricle. This collection of cells constitutes the arcuate nucleus in lower mammals and the infundibular nucleus in man. These cells send their axons down into the underlying neurohypophysis—in man the median eminence proper and the pituitary stalk, and perhaps even the neural lobe of the pituitary. Here these axons make contact with the capillaries of the so-called pituitary portal system, composed both of the long portal vessels from the upper neurohypophysis (median eminence and upper stalk) and of the short portal vessels from the lower neurohypophysis (the lower stalk and neural lobe). These axons are in a position to discharge specific chemical mediators into the portal vessels; through these the mediators, now generally termed "releasing factors," are conducted to the adenohypophysis, which they affect. The additional importance of the portal vessels as the major or sole source of blood supply to the adenohypophysis should also be kept in mind. The elimination of such vessels results in pituitary infarction, depending in degree on the level of the transection and the species.

As a result of chemical stimulation the adenohypophysis then discharges one or another of its hormones. Some of these act on the target tissue directly, as does growth hormone; others act indirectly by causing the release of hormone from some target gland, as in the case of the adrenals or gonads. Indeed, it is possible to classify neuroendocrine control mechanisms generally into first-, second-, or third-order, depending upon the number of endocrine links between brain and final destination. Direct action of a brain hormone upon its target, as in the action of vasopressin on the kidney, is an example of a first-order mechanism. The chain involving the action of a brain hormone or releasing factor upon the anterior pituitary to produce release of somatotropin, which then acts on the target tissue, is a second-order one. The addition of still another link in the chain, as in the case of the anterior pituitary hormone acting through a target gland such as the adrenal, constitutes a third-order chain. The presence of these extra steps long caused the pituitary to be looked upon as the primary controller of all other endocrine gland functions; it now appears that the adenohypophysis is more of a mediator between brain and target gland in these instances, but one that may contribute important elements of amplification and stability to the control network.

The existence of the specific chemical substances involved in this control, one for each adenohypophysial hormone, has been suspected ever since the accumulation of evidence for chemical control of the adenohypophysis via the portal system and the discovery of neurosecretory cells. At the same time, evidence for significant control of the pituitary by direct innervation has never been strong or convincing. Now direct evidence is available for the existence of all the releasing factors. Moreover, this chemical control need not necessarily be purely excitatory or stimulatory; one hormone at least, prolactin, appears to be under inhibitory control of the hypothalamus, and a specific inhibiting factor has been found in median eminence tissue. The neurosecretory cells and their axonal processes are somewhat analogous to the somatic or autonomic motoneurones. Taken together with the means of delivery to the adenohypophysis, the portal system, they comprise the final common pathway from brain to pituitary.

Direct evidence about the location and identity of the elements subserving detector and set-point function is more difficult to obtain, and some present experimental results are conflicting or suggest multiple

sites. The simplest hypothesis would place them at or within the very neurosecretory neurones that produce the releasing factors and constitute the final common pathway, but the rigidity of such a system, the discovery of hormone-sensitive sites elsewhere in the brain and, to a degree, the existence of states of hyperfunction or other insensitivity to feedback suggest that the sensors and effectors are anatomically separate; the same may be said for the set-point elements. Lesion experiments have shown clearly that the median eminence and certain regions of the ventromedial hypothalamus and the preoptic region must be intact for the compensatory glandular hypertrophy and the re-establishment of normal hormone levels that normally follows partial destruction of any of the target glands to occur. Furthermore, a similar interference with this mechanism results from the local hypothalamic implantations of crystals of target gland hormone or fragments of target gland tissue. Interpretation of this latter sort of evidence is confounded by the possibility of transfer of the hormone to the pituitary itself via the portal circulation, and by the high and possibly unphysiological hypothalamic concentrations of hormone that result. Also, in some instances (thyroid, for example) local implantation of thyroid hormone directly into the pituitary gland has an inhibitory action. The actual selective localization of one radioactively labeled hormone, estrogen, within the anterior hypothalamus and preoptic region has recently been demonstrated histologically. It is probably fair to conclude that the feedback mechanism includes not only the pituitary gland but the final common pathway consisting of median eminence, stalk, and portal vessels, and also certain hormone-sensitive regions of the surrounding ventral hypothalamus, preoptic region, and perhaps even midbrain. This complex is involved in the compensatory increase in pituitary gland stimulation that results from reduced hormone levels in the peripheral blood. The adenohypophysis itself also may be directly inhibited by elevated hormone levels, but the physiological significance of this mechanism is unproved.

The comparator might be separate also, but could just as well reside within the very neurones of the infundibular nucleus that function as part of the effector apparatus. Amplification between comparator and effector is then obtained by the relationship between the quantity of releasing factor discharged per unit of neural activity and the sensitivity of the adenohypophysial cells to the releasing factors. As mentioned, an additional stage of amplification may then be introduced by the

pituitary itself in instances where its hormones act indirectly through other endocrine glands. Translation of the error signal into an effective response, the work of the control device, is incorporated into these same stages.

The function of maintaining chemical homeostasis within the internal environment is somewhat analogous to the function of maintaining the muscle tone, regardless of posture, of the neuromuscular system. In the same way, the necessary mechanism—the feedback loop involving hormone levels and the sensors in the ventral hypothalamus and the final common pathway, the neurosecretory neurone, and portal system—is likewise analogous to the muscle spindle, the γ-loop, and the neuromuscular unit of the spinal cord.

Neuroendocrine Reflexes

Homeostasis is only one of several tasks performed by the neuroendocrine system. Another class, that of stereotyped responses to specific stimuli, is more analogous to the better-known reflex responses of the neuromuscular or autonomic systems in which some sensory signal from the environment, exogenous or endogenous, elicits a rather transient reaction. The response itself may be an all-or-none type or may be graded, within limits, in proportion to the strength of the stimulus. Throughout the response period homeostasis is sacrificed, but it is reimposed at the cessation of the stimulus or as a result of adaptation or some other self-limiting feature if the stimulus is prolonged or repeated. A few of the many known examples of such neuroendocrine reflexes include reflex ovulation in response to specific olfactory, visual, or tactile stimuli, the release of ACTH to various forms of stress, of oxytocin to suckling, and of vasopressin to a fall in blood pressure.

Disorders involving neuroendocrine reflex mechanisms manifest themselves by a depression or absence of the expected response, and may result from damage or destruction to the reflex circuit at almost any point in its course. In any event, recognition of a depressed or absent neuroendocrine reflex requires a special search and the employment of procedures specifically designed to elicit them. Relatively few such procedures of much practical clinical value are presently available. Among these might be mentioned the antidiuretic response to tilt-table hypotension, and the ACTH response to natural disease processes or to administration of stressors such as pyrogens. The scarcity of useful

clinical tests in this area is partly due to insufficient exploitation of the possibilities; it is probably even more the result of the fact that man, unlike lower animals, has made himself largely independent of stereotyped reflex responses in all spheres. Such responses play a small role in his biological economy, and the few that persist are of scant localizing value.

The anatomical substrate for neuroendocrine reflexes is far more widespread throughout the nervous system than that of homeostasis. Its efferent limb includes the final common pathway between hypothalamus and the adenohypophysial effector mechanism, and a common site for effective lesions is the hypothalamus, where the pathways all converge toward the median eminence. Here such disorders may present themselves in relatively pure form or be associated with disorders in homeostasis as well. Lesions elsewhere can have the same effect on reflexes but, except for those of the sense organs themselves, they must ordinarily be rather extensive in order to produce a discernible effect; such lesions are usually associated with other, more serious manifestations of nervous-system disease. The reflex afferent limb includes such sensory receptors and afferent pathways—in the spinal cord, brainstem, as well as the visual and olfactory projections—as may be involved in each of these very different responses. Thus there is reason to implicate the pyriform cortex and amygdala in some of the olfactory reflexes, and the brainstem reticular core in the response to pain, stress, and hypotension. Ultimately, these afferent messages converge upon the ventromedial hypothalamus. The way in which they are sorted out and recombined before reaching this destination is largely the province of general neuroanatomical and neurophysiological investigation, and it should be pointed out that the neuroendocrine response is usually only one of a constellation of coordinated muscular, autonomic, and endocrine responses to such stimuli.

Complex Neuroendocrine Responses

In this final category belongs a rather mixed group of responses involving the neuroendocrine system that are clearly too complex or varied to be considered primarily reflex or homeostatic. They are more analogous to the postural or locomotory functions of the somatic nervous system.

Some of these are characterized by an intermittent or even periodic

or rhythmic resetting of the required hormone level or of some variable controlled by it. Devices with a changing set point are generally termed servomechanisms and, like the regulators concerned with homeostasis, they also involve a feedback loop consisting of sensors, a set-point device, comparators, and corrective apparatus. They require, in addition, a mechanism for changing the set point. Moreover, there are practical differences in design between regulators and servomechanisms, at least to the extent that the former emphasize stability, the latter responsiveness. In the neuroendocrine system rapid and complex changes in set point, like those characteristic of such neuromuscular responses as visual tracking, are not required. Instead we are dealing either with the slow readjustments of set point such as occur in the higher levels of thyroid hormone in response to cold and in seasonal cstrus in certain mammals, or with steady rhythmic changes such as the human menstrual cycle.

To these simpler instances of readjustment or rhythmic modulation must be added the more complex combinations of hormonal readjustments: alterations in the endocrine profile that can result from major emotional or environmental changes; or the complex temporal sequences of endocrine changes occurring during growth and maturation and, in lower animals, as a result of seasonal changes. Here not one but many sensory pathways may be involved, sometimes over long periods of time. Moreover, they are complex and their endocrine element may be only a small part of the total response.

Disorders in these spheres are apt to be particularly subtle and complex, defying easy diagnosis. Some of the simpler levels of dysfunction such as the absence of the thyroid response to cold can be investigated, but this is impractical. Certain of the cyclic or sequential mechanisms are quite sensitive to derangement, and the consequences obvious or easily detected. Menstrual irregularities and an abnormal diurnal corticoid cycle are two examples; some instances of delayed or advanced puberty or disturbances in growth are others. Here too, however, the human species is less dependent for survival on complex neuroendocrine adjustments than are lower animals, where such adjustments are critical in maintaining the balance between energy conservation and growth and reproduction. As a result they are apt to be underdeveloped, dominated by higher levels, and hard to characterize, even for the normal; this makes their practical application difficult.

Much of the anatomical substrate for the servomechanisms can be shared with that of the homeostatic regulators, but some means for changing the set point must be provided in addition. This may involve certain sensory pathways such as those responding to seasonal changes in light, local hypothalamic receptors for temperature or, sometimes, rhythmic timing mechanisms, some of whose rhythmicity may be inherent in the feedback loop itself. Besides the necessary afferent pathways, large portions of the medial hypothalamus seem to be involved in these functions. There appears to be a significant amount of diffuseness and overlap between the hypothalamic zones related to each of the respective adenohypophysial hormones, however, and there are also important species differences. How discrete such areas are in the human hypothalamus is difficult to assess, but the entire region is so small that bilaterally symmetrical lesions arising from natural disease processes and placed in just the critical location are hardly to be anticipated.

One such mechanism, the subject of recent investigation, may be taken up with profit in greater detail. This is the diurnal cyclic fluctuation in adrenal cortical hormone blood levels, characteristically high early in the morning and falling steadily during the afternoon and evening. The highest rise actually occurs during sleep and can be shifted along with a change in sleep rhythm;[49] it can also be diminished or eliminated by sleep deprivation.[46] In a recent study, the sharpest rises were found to occur during the latter half of a night's sleep period. Because of the periodicity and time of occurrence, the authors suggest a possible relationship of the corticoid rise to activated (REM) sleep periods.[60] It has also been shown that the ACTH response to metopyrapone disinhibition is greatest during the sleeping hours and greatly suppressed during wakefulness, suggesting a marked readjustment of set point between waking and sleeping, or a virtual exclusion of the homeostat during the day.[41] The importance of sleep in this circadian corticoid rhythm implicates the anatomical substrate of sleep in the pontomesencephalic reticular formation of the brainstem, the thalamus, in the medial forebrain bundle, and in other basal forebrain structures. Experimentally, the daily corticoid cycle has been altered following lesions of the fornix in the monkey,[42] and abolished after lesions of the anterior hypothalamus in the rat.[55]

Handling of the most complex and coordinated neuroendocrine problems is actually a function of a large proportion of the entire brain

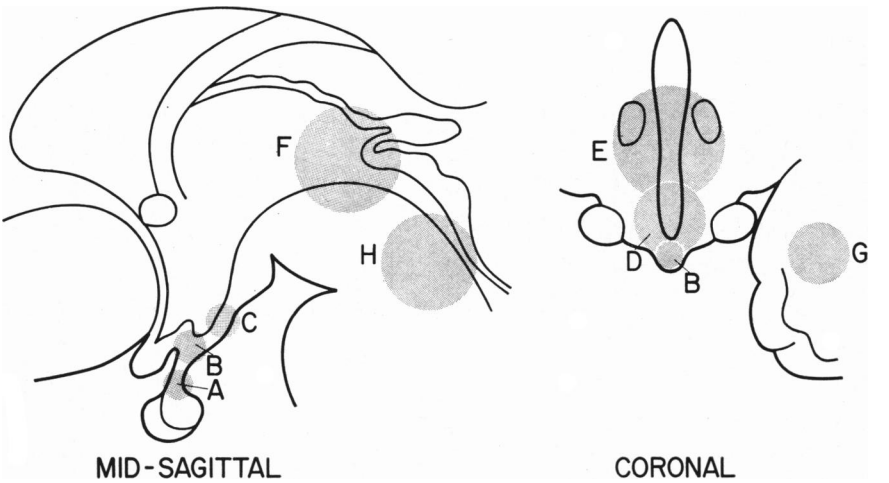

Fig. 1

in lower forms; in man a smaller fraction is involved, but the limbic system, broadly defined, must be added to the hypothalamus, brainstem, and specific sensory pathways as part of the necessary substrate. Indeed evidence is accumulating that the pineal gland also plays a significant role in these mechanisms, and future considerations of this subject will doubtless include it as its function is further clarified.

Neuroendocrine Syndromes

In the foregoing those functional divisions of the neuroendocrine system affecting adenohypophysial performance have been outlined, and it has been convenient to epitomize each class of function, discuss its probable manner of dysfunction, and then conclude with a consideration of its anatomical substrate. In taking up individual syndromes this order will have to be reversed; the relevant disease entities tend to attack one particular locus or another, so that it is more rational to take up individual anatomical sites, especially those most vulnerable to disease, and then outline the signs and symptoms that would and do result from disruption of function, drawing upon the previous section for explanation and support. Each syndrome will then be concluded with a list of actual clinical conditions most commonly responsible.

Some qualifications are in order, however. While our previously delineated functional schema might lead us to predict the existence of a

group of distinct, mutually exclusive syndromes, each with its clear-cut etiological process, we must be prepared to accept something less rigid. Many disease processes produce incomplete destruction, with poorly defined syndromes as a result; others, because of a multiplicity of lesions, may affect several anatomical sites simultaneously, compounding the clinical picture. If the lesions are irregular or asymmetrical their effects will be somewhat unpredictable, because the bilateral symmetry of the hypothalamo-pituitary system requires bilateral damage before a deficit becomes manifest. Many conditions, especially neoplasms, are progressive, and the clinical syndrome is clearest early in the course of the disease. Here a careful history, enumerating the sequence of onset of various symptoms and signs, is helpful in reconstructing the probable nature and original site of the lesion. Finally, we must also recall the special obstacles to clinical neuroendocrine investigation outlined in the *Introduction.* As a consequence, the anatomical separation and discreteness of the lesions and the distinctness of their respective syndromes is necessarily somewhat artificial in the following.

Suprasellar Lesions (Lesions of the Infundibulum and Stalk)

Total lesions. Total lesions situated in this region are in a position to destroy the final common pathway completely, and by so doing abolish all the neuroendocrine functions that depend upon hypothalamic control of the adenohypophysis—homeostatic, reflex, and complex. Such lesions are rare, and the following description is partly a composite one. Within the homeostatic sphere, one finds diminished levels of the various pituitary trophic hormones (with the exception of prolactin) and those of their target glands. The extent to which each is affected relates in turn to the extent to which it is dependent upon hypothalamic control. FSH and LH drop to very low levels, gonadal function all but ceases, and the gonads atrophy; the only exception is LTH or prolactin, which is produced to excess. ACTH drops to low levels, adrenal atrophy sets in, and the secretory activity of the adrenals, although still measurable, falls to levels requiring replacement therapy. Thyroid function diminishes more gradually, and hypothyroidism, which may or may not justify replacement therapy, results. Somatotropin falls to very low resting levels and insulin sensitivity rises, and the growth-hormone responses to hyper- and hypoglycemia are virtually absent as well.[50] Responses to disruption of homeostasis, such as those of the dexametha-

sone suppression and the methopyrapone disinhibition tests, are absent. Naturally abolished too are the neuroendocrine reflexes, including the ACTH response to stress. The more complex responses, such as the menstrual cycle and the diurnal plasma corticoid cycle, are absent as well. The picture is one of an unresponsive endocrine system operating at a low and partially inadequate basal level.

Indeed, the picture closely resembles panhypopituitarism of pituitary origin, and the differential diagnosis can be quite difficult. The obvious way to distinguish between primary pituitary failure and pituitary insufficiency secondary to hypothalamic failure is to administer the various hypothalamic releasing factors systemically in doses adequate to stimulate the pituitary by this route. A positive response would affirm the capacity of the pituitary to respond and fix the blame on the hypothalamus; a negative (absent) response would implicate the pituitary itself, provided the adrenal response to ACTH, for example, was still present. This sort of test has been attempted, the first reported series involving the use of an intravenous infusion of posterior pituitary extract believed to be contaminated with CRF. (It should be pointed out, however, that vasopressin itself has intrinsic CRF activity and that, in high doses, it has a direct stimulating effect on the adrenals and thyroid.) An increase in urinary corticoid excretion was obtained in normals[7] but not in patients with hypothalamo-hypophysial lesions,[8] yet little difference was obtained between diseases believed to be primarily hypothalamic and those assumed to be of pituitary origin. In another series, similar postpituitary infusions were employed in four cases of panhypopituitarism of suspected hypothalamic origin and increases observed in urinary and plasma hydroxycorticosteroids and radioiodine uptake, but not (in one instance) FSH.[48] More recently, a partially purified CRF preparation has been used instead.[9] A positive response occurred in one patient with temporal lobe seizures. A negative response to CRF was obtained in one case of basal meningitis; two others who also failed to respond to CRF did respond to methopyrapone, however, and these authors were forced to assume that their CRF doses must have been close to threshold. The results to date have been far from clear-cut, and it is apparent that the successful application of this promising test, and others like it, will have to await the availability of adequate amounts of reasonably potent and specific releasing-factor preparations suitable for human administration.

High versus low lesions. There are some important distinctions to be made between interruption of the final common pathway low at the level of the junction of the pituitary stalk with the gland, or high at the level of the infundibular recess, i.e., the median eminence. The neurosecretory processes of the infundibular nucleus enter the median eminence and stalk and descend for varying distances. Likewise, separate arterioles enter the median eminence, the stalk, and even the neural lobe, ramify locally, and then leave to enter the adenohypophysis as long or short portal vessels, depending on their site of origin. High lesions tend to interrupt most or all of the neurosecretory axons or even destroy their nuclei of origin. Many portal vessels that enter the stalk or pars nervosa below the lesion will remain intact, though denervated, and the adenohypophysial blood supply will remain adequate. Low lesions are located distal to the site of termination of most of the neurosecretory axons (the major exceptions being those traveling to the pars nervosa and concerned with vasopressin and oxytocin secretion), so the neural link of the final common pathway will retain its anatomical integrity. These lesions, however, will interrupt virtually all of the portal vessels on their way to the adenohypophysis, with the exception of a few short ones entering directly from the neural lobe, which has been denervated anyway. Substantial infarction of the adenohypophysis results if this is done abruptly, as in pituitary stalk section.

Thus the high lesions, by interrupting or destroying the neural link of the pathway, result in loss of all the various releasing factors, as well as loss of vasopressin and oxytocin, producing permanent diabetes insipidus in addition to the various adenohypophysial deficits. On the other hand, the pituitary gland and its blood supply are intact, and it is still in a position to carry out any secretion that is independent of or was inhibited by hypothalamic control, including the response to exogenous releasing factors.

Such lesions (Figure 1B) produce a picture corresponding to total destruction of the final common pathway, as described above, but lesions confined to this area, confirmed at autopsy and truly complete, are quite uncommon, and most of the few reported cases occurred before the era of endocrine tests and replacement therapy. Metastatic pinealomas, which seed to the infundibular recess of the third ventricle, are perhaps the commonest cause, and a clinical picture including hypogonadism, probably hypoadrenalism, hypothyroidism, and growth-

hormone deficit, in association with diabetes insipidus, has been described. [2, 3, 6, 22, 30, 45, 51] Depending on its site of origin and direction of growth, a primary glioma of the optic chiasm or hypothalamus may also present primarily as an infundibular lesion; indeed a glioma specific to this region, the infundibuloma, has been described by Globus.[26]

Low lesions, best exemplified by cases of surgical stalk section (Figure 1A), interrupt the vascular link of the final common pathway, the pituitary portal system, preventing the delivery of the releasing factors by this route and at the same time producing some degree of anterior pituitary infarction. The neurosecretory neurones are not destroyed and can still release their products into the general circulation. For this reason, diabetes insipidus tends to be mild and, with any regeneration of the neurosecretory terminals in the stalk and median eminence, transient. It is also quite possible that certain retained anterior pituitary functions result from the action of releasing factors that find their way to the pituitary, greatly diluted, via the general circulation. Indeed, some residual ACTH response to stress has been reported,[58] and CRF can be detected in the peripheral blood of hypophysectomized rats.[11] The pituitary infarction, which is variable and followed by some regeneration, adds an element of unpredictability and instability to the picture of adenohypophysial deficiency. Thus the picture is similar to that of high lesions, except that diabetes insipidus is less prominent or absent, and adenohypophysial deficit somewhat more variable and less permanent.[13, 15, 16, 18, 38, 39, 52, 58]

It is even possible to distinguish a picture of intermediate stalk interruption, as exemplified by Dandy's classic case.[12] The stalk was divided at midpoint under direct vision during the course of a chiasmal exploration and no barrier was interposed; permanent diabetes insipidus resulted, but there were no other endocrine repercussions. The patient subsequently bore several children. Presumably the section was high enough to involve most of the supraopticohypophysial system and thus eliminated vasopressin secretion, and was also high enough to avoid pituitary infarction. On the other hand, it was not so high as to destroy the infundibular nucleus and the various releasing factors. One must presume that the portal vessels regenerated; they have demonstrable capacity to do so, no barrier was interposed, and pituitary infarction must have been negligible. Releasing factors can also reach the pituitary

by way of the general circulation, as mentioned, but not in amounts sufficient to maintain normal basal gonadotropin levels, much less reestablish fertility. Thus had a barrier been interposed at operation in Dandy's case, preventing portal vessel regeneration, the resulting clinical picture would probably have resembled that of low stalk section, except for more severe diabetes insipidus.

Low lesions of the final common pathway are not common clinically. They are encountered after deliberate pituitary stalk section, as performed for cancer or diabetic retinopathy, provided that the operation has been meticulously complete technically and has included interposition of a barrier to prevent regeneration of the portal vessels. Something similar may result from avulsion of the pituitary stalk in severe closed head injuries. The location in both cases can be either low or intermediate depending on technique or accident. Tumors in this region may produce the same result; of these the craniopharyngiomas are the most common cause. Other neoplasms that can produce a similar picture include the suprasellar extension of pituitary adenomas and suprasellar meningiomas. Still less common causes, particularly nowadays, are inflammatory conditions of the basal meninges, especially tuberculous or luetic, and granulomatous lesions such as sarcoid or the lipoidoses. An aneurysm of the circle of Willis occasionally expands in this direction.

Incomplete lesions. More commonly, the clinical picture from many such lesions is an incomplete one. This is especially true of the tumors, which grow slowly, allowing time for compensatory processes to operate. Also, the margin of safety in this system is high, and functional tissue is often displaced rather than destroyed. Autopsy confirmation of the lesion, when available at all, is not apt to be helpful beyond localization of the lesion to the general region of the hypothalamus.

In such cases, symptoms appear in order of function vulnerability, primarily as gonadal deficiency, which manifests itself as amenorrhea, impotence, or sexual infantilism, depending on age and sex of the patient.[4] In children, this condition combined with obesity of ventromedial hypothalamic origin constitutes the classical Fröhlich's syndrome[21] (Figure 1D).

More modern studies of adrenal function have demonstrated a derangement of diurnal rhythms in a number of cases with lesions in this area,[33] although in some apparently similar cases the rhythms persist.[29, 48] In a few cases tested for dexamethasone suppression, it has been pres-

ent.[48] The methopyrapone disinhibition test has been explored more extensively. It is apt to be abnormal in cases of primary pituitary disease, even when the baseline values are normal.[10, 36, 40] Abnormal findings have also been reported in cases with lesions in the region of the infundibulum, usually cases with other good evidence of endocrinopathy, but normal responses are commoner.[9, 24, 25, 27, 29, 34, 36, 40, 48] Thus it appears that these adrenal-mediated responses are more resistant to derangement than those involving the gonads, that lesions complete enough to produce measurable abnormality are in the minority, and that most of these have obvious associated endocrinopathies.

Galactorrhea. Another less common result of partial lesions of the infundibular region deserves special mention. This is the syndrome of pathological lactation or galactorrhea, usually associated with amenorrhea and uterine atrophy and termed the Chiari-Frommel syndrome. As mentioned, prolactin is under inhibitory control; the release of all or even a portion of the adenohypophysis from hypothalamic restraint will result in overproduction of prolactin by the disinhibited portion of the gland. To be manifest, the excess prolactin must act upon a hormonally prepared mammary gland. Such preparation includes not only estrogen and progesterone but at least permissive levels of adrenal and growth hormone as well. Thus the syndrome most commonly appears after those partial lesions that release enough pituitary gland from inhibition to provide the elevated prolactin levels but, at the same time, spare enough of the final common pathway so that hypothalamic stimulation of the pituitary will yield at least permissive levels of gonadotropin, ACTH, etc. Sometimes the syndrome appears to be functional; it was originally described as commonest in young, undernourished, but otherwise well postpartum women.[44] Sometimes it is completely idiopathic and is associated with mild obesity and hirsutism; other cases have demonstrable pituitary adenomas, and the possibility that the tumors themselves secrete autonomously must be considered.[20, 28] It is a characteristic result of pituitary stalk section, where hormonal replacement therapy probably plays the permissive role.[16] It has also been described sporadically in association with a variety of other sellar and suprasellar lesions. Undoubtedly it is much commoner than has been reported since, in the absence of oxytocin secretion, the galactorrhea is apt to be overlooked unless the milk is expressed manually.

Para-Infundibular Lesions

Lesions in the general region of the infundibulum may be in a position to interrupt certain of the tracts impinging upon the final common pathway while preserving the pathway itself; they will be termed para-infundibular. In primates such as man, because of the flexion of the forebrain on the brainstem and the forward direction of the pituitary stalk, most of this area is behind or to the sides of the stalk; little but optic chiasm is in front. Lesions in the para-infundibular zone are potentially in a position to disrupt the homeostatic mechanisms, especially the sensor or set-point elements, while sparing the efferent limb. As postulated in the section on general neuroendocrine functions, this could result in independence of feedback and even unmodulated hyperfunction.

In these cases with para-infundibular lesions it is primarily the feedback and homeostatic mechanism that is damaged, but the final common pathway need not be otherwise deafferented. Neuroendocrine reflexes thus can and do persist, especially if the stimulus is strong enough. The same may be said for complex neuroendocrine responses provided that the lesion is strictly confined to the para-infundibular region and the rest of the hypothalamus is spared.

Lesions in this region, especially just behind the median eminence (Figure 1C), have long been recognized as leading to precocious puberty in both male and female children, in whom the commonest lesion is hamartoma. While a secretory function for such tumors has been postulated as the source of the precocious puberty—through the presumed overproduction of gonadotropin-releasing factors—this has never been directly demonstrated. Furthermore, a wide variety of other lesions in the same location with no histological features in common (e.g., pinealomas, ependymomas, neurofibromas, gliomas, metastases, tuberous sclerosis, inflammatory conditions, and even simple ballooning of the retroinfundibular or premammillary recess of the third ventricle from advanced internal hydrocephalus) have all produced the syndrome in one case or another.[37, 57, 59, 62] Stimulation of the gonadotropin-releasing factor production by an irritating effect of the lesion has also been suggested, but again it is difficult to understand why other associated consequences of irritation, including seizures, as well as evidence of irritation from these same lesions elsewhere, are all so uncommon. The

appearance of regular menstruation, which is occasionally observed in these cases, is particularly difficult to explain solely on the basis of pathological irritation. On the other hand, it must be admitted that the amount of hypothalamic damage in these cases is sometimes surprisingly small.[57] Precocious puberty has been produced in experimental animals by making hypothalamic lesions.[54, 62] In at least some and perhaps all such cases, I should prefer to implicate damaged negative feedback; indeed a special state of high sensitivity to inhibition—a low set point—may be all that normally prevents sexual maturation in infancy or childhood.

Damaged feedback control could conceivably account for some of the other instances of endocrine hyperfunction known to be associated with an excess of pituitary drive, including hyperthyroidism and Cushing's syndrome. In the case of the latter syndrome, after eliminating cases of primary adrenal origin and those with malignant tumors producing an ACTH-like substance, one is left with a class of patients in whom the excess ACTH is of pituitary origin and in whom dexamethasone suppression is clearly subnormal, the diurnal pattern disrupted, and the response to methopyrapone excessive. Some of these cases turn out to have basophilic pituitary adenomas, but others do not, and a damaged feedback mechanism has been postulated.[14, 36] Obvious lesions of the para-infundibular region have not been demonstrated in this last group of cases, however, so that the matter remains unsettled.

Derangements in feedback control have been objectively demonstrated in a few patients suffering from lesions in this region. Using the dexamethasone suppression test, a defective response was observed in one patient with cerebral atrophy and precocious puberty, suggesting defective feedback in both adrenal and gonadal spheres.[48] In another case, however, precocious puberty from an optic nerve glioma was associated with a normal methopyrapone test,[24] demonstrating that these defects need not go together. Of the remaining patients with reported absent responses to methopyrapone, many are unsuitable for inclusion under this heading, since there was evidence of basal endocrine insufficiencies, implicating the final common pathway as well. In others, the etiological process was sometimes rather diffuse (degenerative disease, head injury, encephalitis, epilepsy, etc.), but in the absence of other endocrinopathy, the hypothalamic feedback regions are reasonably suspect as sites of functional failure.[10, 24, 27, 35, 43, 48]

Intrahypothalamic Lesions

It is possible for lesions to occur within the hypothalamus that spare both the infundibular and para-infundibular regions, at least for some time. For this reason, homeostatic neuroendocrine mechanisms may persist intact. If the ventral hypothalamus is effectively deafferented, neuroendocrine reflexes will be abolished, but few lesions are that complete, and some responsiveness generally persists. Cases have been described showing amenorrhea with comparatively normal gonadal steroid excretion levels, suggesting that the effector mechanism was intact and working but that the cycle-controlling one was not. A similar condition is encountered in animals with hypothalamic lesions and is termed constant estrus. It is not yet clear, however, how dependent the cycles are upon hypothalamic hormonal feedback, and where these zones are located in humans. It is consequently uncertain whether this syndrome should be classed with the other para-infundibular syndromes characterized by release from feedback inhibition or belongs in a separate category.

Hypothalamic diseases taken as a group form such a heterogeneous aggregate by both etiology and localization (the latter often being diffuse or insufficiently specified) that after subtraction of the better-localized infundibular and para-infundibular groups one is left with a group about which only a few cautious generalizations can be made. Gonadotropin functions are most commonly affected, as suggested in the previous paragraph; thyroid function much less so, and adrenal function only very rarely.[4, 31] This may be partly a consequence of pituitary reserve, which shows the same order of vulnerability following progressively graded partial hypophysectomies.[23] It is probably more related to the fact that these lesions encroach upon the infundibular region and that the deficiencies simply reflect pituitary dependence upon hypothalamic releasing factors, as discussed previously. It may also be indicative of the fact that, beyond simple homeostatic and occasional reflex (stress) functions, clinical disorders of adrenal and thyroid function are relatively unimportant or tend to be overlooked; this is especially true of subclinical hypothyroidism and the capacity of the adrenals to respond to stress.[31] The same is not so true of gonadotrophic function, especially in the female.

More characteristic of intrahypothalamic lesions is the association of

the endocrinopathies with other disorders, especially of affect, consciousness, energy metabolism, and autonomic functions; thus diabetes insipidus and hypogonadism are commonly associated with obesity and somnolence, especially with lesions of the ventromedial hypothalamus.[4] Emaciation is also encountered, particularly with bilateral lateral hypothalamic damage or, paradoxically, bilateral periventricular destruction,[5] and both have also been observed in experimental animals. Lesions more dorsally located (Figure 1E) are apt to be associated with emotional lability, dysthermia, convulsions, autonomic disturbances, and alterations in consciousness, not infrequently in the absence of any obvious endocrinopathy, but these syndromes are beyond the scope of the present discussion.

Extrahypothalamic and Diffuse or Unlocalized Lesions

No clear-cut endocrine syndromes resulting from purely extrahypothalamic lesions appear to have been described. Instead, one finds isolated abnormalities, usually associated with limbic or brainstem disorders and, not uncommonly, with epileptic seizures. Abnormalities in the diurnal corticoid rhythm have been observed sporadically in cases of pretectal disease (Figure 1F) and in temporal lobe conditions associated with seizures (Figure 1G) whereas such abnormalities are usually absent in diseases of the cerebral or cerebellar hemispheres.[32, 33, 48] Not surprisingly, it is apt to be disrupted by any brain injury that results in significant disturbances of consciousness.[17, 49] While the diurnal variations are often absent after severe head injury, the methopyrapone disinhibition and the dexamethasone suppression tests are often abnormal as well, suggesting local hypothalamic damage and diminishing the localizing value of such cases even when disturbances of consciousness point to upper brainstem involvement (Figure 1H).[43]

Animal experiments have clearly shown that the ACTH response to trauma is deficient or absent if the traumatized tissue was deafferented previously or as part of the accident, and something similar may obtain in cases of spinal-cord injury in man. A similar defect in the stress response is also seen experimentally following large lesions of the brainstem reticular formation, and this too may have a clinical counterpart in cases of head injury associated with hemorrhagic or pressure necrosis of the midbrain in man. This subject has been explored in a preliminary way, but because of the heterogeneity of clinical trauma

patients, no conclusions can be drawn as yet.[19, 47, 61]

In an interesting series of three children with seizures of temporal lobe (and presumably limbic) origin, precocious puberty was seen in two, and delayed, irregular menses associated with hirsutism in the other.[1] Other lesions were presumably absent. Although in seizure cases the abnormality may be rather widespread, these cases raise interesting possibilities about the influence of limbic modulation upon gonadotropic function in man, at least under pathological conditions. It is only fair to point out, however, that most patients with limbic seizures do not have such endocrine manifestations; also the modifying effects of anticonvulsant medication must always be kept in mind. Moreover, such seizures spread quickly throughout the limbic system and even beyond, and it is difficult to ascertain where the disease process is acting and whether by excitation or destruction.

Recently a syndrome has been recognized characterized by excessive growth and certain acromegalic features during early childhood in association with mental retardation, motor incoordination, and macrocephaly with enlarged cerebral ventricles. These children had a history of difficult birth, but none had any evidence of pituitary tumor. The authors suggested a disorder of growth hormone control secondary to brain injury or abnormality, but the etiology remains speculative and no further localization is possible yet.[56]

A discussion of the diffuse processes leading to endocrine abnormalities would perhaps not be complete without at least a reference to the fact that the over-all profile of endocrine gland activity, as reflected in mean urinary excretion and plasma levels, is under control of the general emotional state of the individual and changes with it.[42] Likewise, it is disturbed in mental disease characterized by excessive or abnormal affective reactions.[53] Such manifestations are probably the result rather than the cause of the mental disorder, but the full implication of these endocrine disturbances linked to emotional and mental disorders has not yet really been assessed.

In the foregoing an attempt has been made to systematize some of the scattered and still rather scanty data on neuroendocrine disorders in man by drawing upon a functional schema based upon experimental findings, and by resorting to analogy between the neuroendocrine system and artificial regulators and servomechanisms where useful. This attempt should aid in putting human neuroendocrine disorders in better

perspective and in indicating how this area lends itself to greater exploitation in the future.

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